

US 04/ 24340

PCT/US 04/24340

28 JUL 2004

PA 1183592

REC'D 10 SEP 2004

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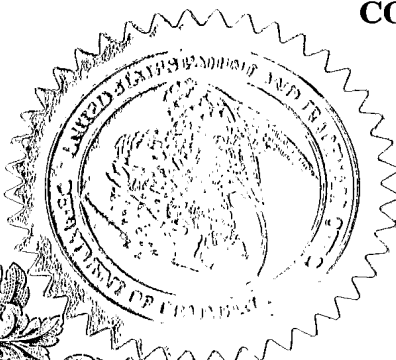
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APPLICATION NUMBER: 60/491,055

FILING DATE: July 30, 2003

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
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FEE RECORD SHEET

08/01/2003 EFLORES 00000012 192570 60491055

01 FC:1005 160.00 DA

PTO-1556
(5/87)

*U.S. Government Printing Office: 2002 — 488-287/69033

07/30/03
1042 U.S. PRO

Date Of Deposit: **July 30, 2003**

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(Type Or Print) **STEVEN OLSZEWSKI**

Signature *Steven Olszewski*

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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

Docket No.			PU60417P1
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TITLE OF THE INVENTION (280 characters max)

INHIBITORS OF AKT ACTIVITY

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ENCLOSED APPLICATION PARTS (check all that apply)

<input checked="" type="checkbox"/> Specification	Number of Pages	44	Total Number of Pages = 45
<input checked="" type="checkbox"/> Abstract	Number of Pages	1	
<input type="checkbox"/> Drawings	Number of Sheets		<input type="checkbox"/> Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

<input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. 19-2570	PROVISIONAL FILING FEE AMOUNT (\$)	\$160.00
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Respectfully submitted,
Signature:

Wayne J. Dustman
Wayne J. Dustman

Date: **July 30, 2003**
Registration No.: **33,870**

☐ Additional inventors are being named on separately numbered sheets attached hereto.

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INHIBITORS OF AKT ACTIVITY

FIELD OF THE INVENTION

5 This invention relates to novel 1H-imidazo[4,5-c]pyridin-2-yl compounds, the use of such compounds as inhibitors of PKB/AKT kinase activity and in the treatment of cancer and arthritis.

BACKGROUND OF THE INVENTION

10 The present invention relates to 1H-imidazo[4,5-c]pyridin-2-yl containing compounds that are inhibitors of the activity of one or more of the isoforms of the serine/threonine kinase, Akt (also known as PKB). The present invention also relates to pharmaceutical compositions comprising such compounds and methods of using the instant compounds in the treatment of cancer and arthritis.

15 Apoptosis (programmed cell death) plays essential roles in embryonic development and pathogenesis of various diseases, such as degenerative neuronal diseases, cardiovascular diseases and cancer. Recent work has led to the identification of various pro- and anti-apoptotic gene products that are involved in the regulation or execution of programmed cell death. Expression of anti-apoptotic genes, such as Bcl2 or Bcl-x_L, inhibits apoptotic cell death induced by various
20 stimuli. On the other hand, expression of pro-apoptotic genes, such as Bax or Bad, leads to programmed cell death (Aams et al. *Science*, 281:1322-1326 (1998)). The execution of programmed cell death is mediated by caspase -1 related proteinases, including caspase-3, caspase- 7, caspase-8 and caspase-9 etc (Thornberry et al. *Science*, 281:1312-1316 (1998)).

25 The phosphatidylinositol 3'-OH kinase (PI3K)/Akt/PKB pathway appears important for regulating cell survival/cell death (Kulik et al. *Mol.Cell.Biol.* 17:1595-1606 (1997); Franke et al, *Cell*, 88:435-437 (1997); Kauffmann-Zeh et al. *Nature* 385:544-548 (1997) Hemmings *Science*, 275:628-630 (1997); Dudek et al., *Science*, 275:661-665 (1997)). Survival factors, such as platelet derived growth
30 factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-I), promote cell survival under various conditions by inducing the activity of PI3K (Kulik et al. 1997, Hemmings 1997). Activated PI3K leads to the production of phosphatidylinositol (3,4,5)-triphosphate (PtdIns (3,4,5)-P3), which in turn binds to, and promotes the activation of, the serine/ threonine kinase Akt, which contains a
35 pleckstrin homology (PH)-domain (Franke et al *Cell*, 81:727-736 (1995); Hemmings *Science*, 277:534 (1997); Downward, *Curr. Opin. Cell Biol.* 10:262-267 (1998), Alessi et al., *EMBO J.* 15: 6541-6551 (1996)). Specific inhibitors of PI3K or

dominant negative Akt/PKB mutants abolish survival-promoting activities of these growth factors or cytokines. It has been previously disclosed that inhibitors of PI3K (LY294002 or wortmannin) blocked the activation of Akt/PKB by upstream kinases. In addition, introduction of constitutively active PI3K or Akt/PKB mutants promotes
5 cell survival under conditions in which cells normally undergo apoptotic cell death (Kulik et al. 1997, Dudek et al. 1997).

Analysis of Akt levels in human tumors showed that Akt2 is overexpressed in a significant number of ovarian (J. Q. Cheung et al. *Proc. Natl. Acad. Sci. U.S.A.* 89:9267-9271(1992)) and pancreatic cancers (J. Q. Cheung et al. *Proc. Natl. Acad. Sci. U.S.A.* 93:3636-3641 (1996)). Similarly, Akt3 was found to be overexpressed
10 in breast and prostate cancer cell lines (Nakatani et al. *J. Biol.Chem.* 274:21528-21532 (1999).

The tumor suppressor PTEN, a protein and lipid phosphatase that specifically removes the 3' phosphate of PtdIns(3,4,5)-P3, is a negative regulator of the PI3K/Akt pathway (Li et al. *Science* 275:1943-1947 (1997), Stambolic et al. *Cell* 95:29-39 (1998), Sun et al. *Proc. Natl. Acad. Sci. U.S.A.* 96:6199-6204 (1999)). Germline mutations of PTEN are responsible for human cancer syndromes such as Cowden disease (Liaw et al. *Nature Genetics* 16:64-67 (1997)). PTEN is deleted in
15 a large percentage of human tumors and tumor cell lines without functional PTEN show elevated levels of activated Akt (Li et al. supra, Guldberg et al. *Cancer Research* 57:3660-3663 (1997), Risinger et al. *Cancer Research* 57:4736-4738 (1997)).
20

These observations demonstrate that the PI3K/Akt pathway plays important roles for regulating cell survival or apoptosis in tumorigenesis.

25 Three members of the Akt/PKB subfamily of second-messenger regulated serine/threonine protein kinases have been identified and termed Akt1/ PKB α , Akt2/PKB β , and Akt3/PKB γ respectively. The isoforms are homologous, particularly in regions encoding the catalytic domains. Akt/PKBs are activated by phosphorylation events occurring in response to PI3K signaling. PI3K
30 phosphorylates membrane inositol phospholipids, generating the second messengers phosphatidyl- inositol 3,4,5-trisphosphate and phosphatidylinositol 3,4-bisphosphate, which have been shown to bind to the PH domain of Akt/PKB. The current model of Akt/PKB activation proposes recruitment of the enzyme to the membrane by 3'-phosphorylated phosphoinositides, where phosphorylation of the
35 regulatory sites of Akt/PKB by the upstream kinases occurs (B.A. Hemmings, *Science* 275:628-630 (1997); B.A. Hemmings, *Science* 276:534 (1997); J. Downward, *Science* 279:673-674 (1998)).

Phosphorylation of Akt1/PKB α occurs on two regulatory sites, Thr³⁰⁸ in the catalytic domain activation loop and on Ser⁴⁷³ near the carboxy terminus (D. R. Alessi *et al.* *EMBO J.* 15:6541-6551 (1996) and R. Meier *et al.* *J. Biol. Chem.* 272:30491-30497 (1997)). Equivalent regulatory phosphorylation sites occur in Akt2/PKB β and Akt3/PKB γ . The upstream kinase, which phosphorylates Akt/PKB at the activation loop site has been cloned and termed 3'-phosphoinositide dependent protein kinase 1 (PDK1). PDK1 phosphorylates not only Akt/PKB, but also p70 ribosomal S6 kinase, p90RSK, serum and glucocorticoid-regulated kinase (SGK), and protein kinase C. The upstream kinase phosphorylating the regulatory site of Akt/PKB near the carboxy terminus has not been identified yet, but recent reports imply a role for the integrin-linked kinase (ILK-1), a serine/threonine protein kinase, or autophosphorylation.

Inhibition of Akt activation and activity can be achieved by inhibiting PI3K with inhibitors such as LY294002 and wortmannin. However, PI3K inhibition has the potential to indiscriminately affect not just all three Akt isozymes but also other PH domain-containing signaling molecules that are dependent on PtdIns(3,4,5)-P3, such as the Tec family of tyrosine kinases. Furthermore, it has been disclosed that Akt can be activated by growth signals that are independent of PI3K.

Alternatively, Akt activity can be inhibited by blocking the activity of the upstream kinase PDK1. No specific PDK1 inhibitors have been disclosed. Again, inhibition of PDK1 would result in inhibition of multiple protein kinases whose activities depend on PDK1, such as atypical PKC isoforms, SGK, and S6 kinases (Williams *et al.* *Curr. Biol.* 10:439-448 (2000)).

It is an object of the instant invention to provide novel compounds that are inhibitors of Akt/PKB.

It is also an object of the present invention to provide pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

It is also an object of the present invention to provide a method for treating cancer that comprises administering such inhibitors of Akt/PKB activity.

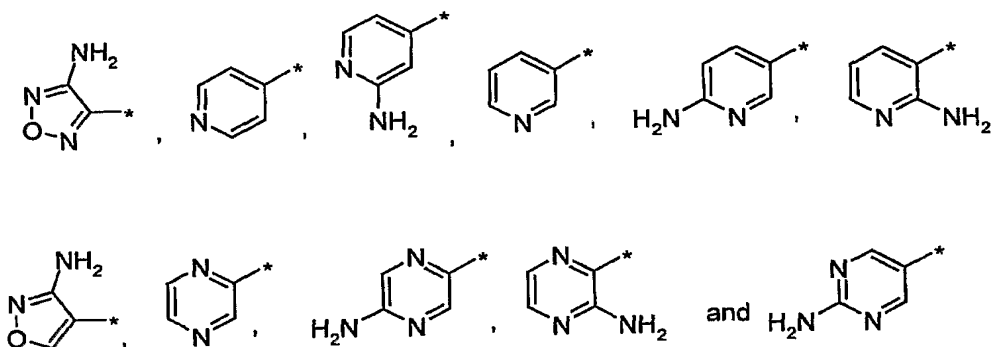
It is also an object of the present invention to provide a method for treating arthritis that comprises administering such inhibitors of Akt/PKB activity.

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180 181 182 183 184 185 186 187 188 189 190 191 192 193 194 195 196 197 198 199 200 201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240 241 242 243 244 245 246 247 248 249 250 251 252 253 254 255 256 257 258 259 260 261 262 263 264 265 266 267 268 269 270 271 272 273 274 275 276 277 278 279 280 281 282 283 284 285 286 287 288 289 290 291 292 293 294 295 296 297 298 299 300 301 302 303 304 305 306 307 308 309 310 311 312 313 314 315 316 317 318 319 320 321 322 323 324 325 326 327 328 329 330 331 332 333 334 335 336 337 338 339 340 341 342 343 344 345 346 347 348 349 350 351 352 353 354 355 356 357 358 359 360 361 362 363 364 365 366 367 368 369 370 371 372 373 374 375 376 377 378 379 380 381 382 383 384 385 386 387 388 389 390 391 392 393 394 395 396 397 398 399 400 401 402 403 404 405 406 407 408 409 410 411 412 413 414 415 416 417 418 419 420 421 422 423 424 425 426 427 428 429 430 431 432 433 434 435 436 437 438 439 440 441 442 443 444 445 446 447 448 449 450 451 452 453 454 455 456 457 458 459 460 461 462 463 464 465 466 467 468 469 470 471 472 473 474 475 476 477 478 479 480 481 482 483 484 485 486 487 488 489 490 491 492 493 494 495 496 497 498 499 500 501 502 503 504 505 506 507 508 509 510 511 512 513 514 515 516 517 518 519 520 521 522 523 524 525 526 527 528 529 530 531 532 533 534 535 536 537 538 539 540 541 542 543 544 545 546 547 548 549 550 551 552 553 554 555 556 557 558 559 560 561 562 563 564 565 566 567 568 569 570 571 572 573 574 575 576 577 578 579 580 581 582 583 584 585 586 587 588 589 590 591 592 593 594 595 596 597 598 599 600 601 602 603 604 605 606 607 608 609 610 611 612 613 614 615 616 617 618 619 620 621 622 623 624 625 626 627 628 629 630 631 632 633 634 635 636 637 638 639 640 641 642 643 644 645 646 647 648 649 650 651 652 653 654 655 656 657 658 659 660 661 662 663 664 665 666 667 668 669 670 671 672 673 674 675 676 677 678 679 680 681 682 683 684 685 686 687 688 689 690 691 692 693 694 695 696 697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713 714 715 716 717 718 719 720 721 722 723 724 725 726 727 728 729 730 731 732 733 734 735 736 737 738 739 740 741 742 743 744 745 746 747 748 749 750 751 752 753 754 755 756 757 758 759 760 761 762 763 764 765 766 767 768 769 770 771 772 773 774 775 776 777 778 779 780 781 782 783 784 785 786 787 788 789 790 791 792 793 794 795 796 797 798 799 800 801 802 803 804 805 806 807 808 809 810 811 812 813 814 815 816 817 818 819 820 821 822 823 824 825 826 827 828 829 830 831 832 833 834 835 836 837 838 839 840 841 842 843 844 845 846 847 848 849 850 851 852 853 854 855 856 857 858 859 860 861 862 863 864 865 866 867 868 869 870 871 872 873 874 875 876 877 878 879 880 881 882 883 884 885 886 887 888 889 890 891 892 893 894 895 896 897 898 899 900 901 902 903 904 905 906 907 908 909 910 911 912 913 914 915 916 917 918 919 920 921 922 923 924 925 926 927 928 929 930 931 932 933 934 935 936 937 938 939 940 941 942 943 944 945 946 947 948 949 950 951 952 953 954 955 956 957 958 959 960 961 962 963 964 965 966 967 968 969 970 971 972 973 974 975 976 977 978 979 980 981 982 983 984 985 986 987 988 989 990 991 992 993 994 995 996 997 998 999 1000 1001 1002 1003 1004 1005 1006 1007 1008 1009 1010 1011 1012 1013 1014 1015 1016 1017 1018 1019 1020 1021 1022 1023 1024 1025 1026 1027 1028 1029 1030 1031 1032 1033 1034 1035 1036 1037 1038 1039 1040 1

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R¹ is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, C₁-C₁₂aryl and C₁-C₁₂aryl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

R⁴ is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally

containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, $-C(O)OR^2$, $-C(O)NR^5R^6$, $-S(O)_2NR^5R^6$, $-S(O)_nR^2$ and protected $-OH$, where n is 0-2,

R^2 is hydrogen, alkyl, cycloalkyl, C_1 - C_{12} aryl, substituted alkyl, substituted cycloalkyl and substituted C_1 - C_{12} aryl, and R^5 and R^6 are independently hydrogen, cycloalkyl, C_1 - C_{12} aryl, substituted cycloalkyl, substituted C_1 - C_{12} aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected $-OH$, or R^5 and R^6 taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1 - C_{12} aryl, substituted alkyl, substituted cycloalkyl and substituted C_1 - C_{12} aryl, and n is 0-2; and

R^7 is selected from hydrogen, $-C(O)NR^9R^{10}$, $-(CH_2)_nNR^9R^{10}$, $-SO_2NR^9R^{10}$ and $-(CH_2)_nOR^8$, where n is 0-2;

R^8 is alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected $-OH$,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1 - C_{12} aryl, substituted alkyl, substituted cycloalkyl and substituted C_1 - C_{12} aryl, and n is 0-2,

5 R^9 and R^{10} are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C_1 - C_{12} aryl, substituted cycloalkyl, substituted C_1 - C_{12} aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acetylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, - $C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, $-NR^2R^3$, nitro, cyano, 10 cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected $-OH$,

or R^9 and R^{10} taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is 15 optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1 - C_{12} aryl, substituted alkyl, substituted cycloalkyl and substituted C_1 - C_{12} aryl, and n is 0-2;

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and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

This invention relates to a method of treating cancer, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB 25 inhibiting compound of Formula (I).

This invention relates to a method of treating arthritis, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

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The present invention also relates to the discovery that the compounds of Formula (I) are active as inhibitors of Akt/PKB.

In a further aspect of the invention there is provided novel processes and 35 novel intermediates useful in preparing the presently invented Akt/PKB inhibiting compounds.

Included in the present invention are pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

- 5 Also included in the present invention are methods of co-administering the presently invented Akt/PKB inhibiting compounds with further active ingredients.

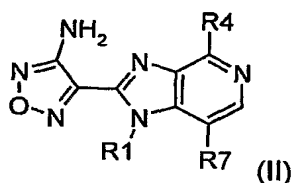
DETAILED DESCRIPTION OF THE INVENTION

This invention relates to compounds of Formula (I) as described above.

- 10 The presently invented compounds of Formula (I) inhibit Akt/PKB activity. In particular, the compounds disclosed selectively inhibit one, two or the three Akt/PKB isoforms.

Included among the presently invented compounds of Formula (I) are those having Formula (II):

15



wherein:

- 20 R¹ is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, C₁-C₁₂aryl and C₁-C₁₂aryl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

30

R⁴ is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of

carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, -C(O)OR², -C(O)NR⁵R⁶, -S(O)₂NR⁵R⁶, -S(O)_nR² and protected -OH, where n is 0-2,

R² is hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and

R⁵ and R⁶ are independently hydrogen, cycloalkyl, C₁-C₁₂aryl, substituted cycloalkyl, substituted C₁-C₁₂aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, -C(O)OR², -S(O)_nR², -C(O)NR²R³, -S(O)₂NR²R³, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH, or R⁵ and R⁶ taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R² and R³ are independently hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and n is 0-2; and

R⁷ is selected from hydrogen, -C(O)NR⁹R¹⁰, -(CH₂)_nNR⁹R¹⁰, -SO₂NR⁹R¹⁰ and -(CH₂)_nOR⁸, where n is 0-2;

R⁸ is alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, -C(O)OR², -S(O)_nR², -C(O)NR²R³, -S(O)₂NR²R³, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH,

where R² and R³ are independently hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and n is 0-2,

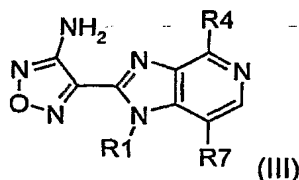
R⁹ and R¹⁰ are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C₁-C₁₂aryl, substituted cycloalkyl, substituted C₁-C₁₂aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, -C(O)OR², -S(O)_nR², -C(O)NR²R³, -S(O)₂NR²R³, -NR²R³, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH,

or R⁹ and R¹⁰ taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R² and R³ are independently hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and n is 0-2;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the presently invented compounds of Formula (I) are those having Formula (III):



wherein:

R¹ is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, C₁-C₁₂aryl and C₁-C₁₂aryl substituted with one or more

substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

5 R^4 is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents
10 selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, $-C(O)OR^2$, $-C(O)NR^5R^6$, $-S(O)_2NR^5R^6$, $-S(O)_nR^2$ and protected $-OH$,
15 where n is 0-2,
 R^2 is hydrogen, alkyl, cycloalkyl, C_1 - C_{12} aryl, substituted alkyl, substituted cycloalkyl and substituted C_1 - C_{12} aryl, and
 R^5 and R^6 are independently hydrogen, cycloalkyl, C_1 - C_{12} aryl, substituted cycloalkyl, substituted C_1 - C_{12} aryl, alkyl or alkyl substituted
20 with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected $-OH$,
25 or R^5 and R^6 taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,
30 where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1 - C_{12} aryl, substituted alkyl, substituted cycloalkyl and substituted C_1 - C_{12} aryl, and n is 0-2; and

R^7 is selected from $-C(O)NR^9R^{10}$, $-(CH_2)_nNR^9R^{10}$, $-SO_2NR^9R^{10}$ and $-(CH_2)_nOR^8$,
35 where n is 0-2;
 R^8 is alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, piperidyl and pyrrolidinyl, each of which is optionally substituted with one

or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected $-OH$,

5 where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1 - C_{12} aryl, substituted alkyl, substituted cycloalkyl and substituted C_1 - C_{12} aryl, and n is 0-2,

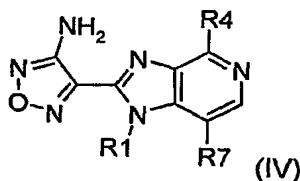
R^9 and R^{10} are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C_1 - C_{12} aryl, substituted cycloalkyl, substituted C_1 - C_{12} aryl, alkyl or alkyl substituted with one or more substituents
10 selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, $-C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, $-NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and
15 protected $-OH$,

or R^9 and R^{10} taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino,
20 methylamino and dimethylamino,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1 - C_{12} aryl, substituted alkyl, substituted cycloalkyl and substituted C_1 - C_{12} aryl, and n is 0-2;

25 and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the presently invented compounds of Formula (I) are those having Formula (IV):



wherein:

R^1 is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy,

amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl
 substituted with one or more substituents selected from the group
 consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen,
 cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1
 5 to 3 heteroatoms substituted with one or more substituents selected from
 the group consisting of: hydroxy, alkoxy, amino, N-acylamino and
 halogen, C₁-C₁₂aryl and C₁-C₁₂aryl substituted with one or more
 substituents selected from the group consisting of: hydroxy, alkoxy,
 amino, N-acylamino and halogen;
 10

R⁴ is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl,
 cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic
 aromatic ring containing from 3 to 16 carbon atoms and optionally
 containing one or more heteroatoms, provided that when the number of
 15 carbon atoms is 3 the aromatic ring contains at least two heteroatoms and
 when the number of carbon atoms is 4 the aromatic ring contains at least
 one heteroatom, and optionally substituted with one or more substituents
 selected from the group consisting of: alkyl, substituted alkyl, aryl,
 substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy,
 20 cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, -C(O)OR²,
 -C(O)NR⁵R⁶, -S(O)₂NR⁵R⁶, -S(O)_nR² and protected -OH,
 where n is 0-2,
 R² is hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted
 cycloalkyl and substituted C₁-C₁₂aryl, and
 25 R⁵ and R⁶ are independently hydrogen, cycloalkyl, C₁-C₁₂aryl,
 substituted cycloalkyl, substituted C₁-C₁₂aryl, alkyl or alkyl substituted
 with one or more substituents selected from the group consisting of:
 alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, -C(O)OR², -
 S(O)_nR², -C(O)NR²R³, -S(O)₂NR²R³, nitro, cyano, cycloalkyl,
 30 substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH,
 or R⁵ and R⁶ taken together with the nitrogen to which they are attached
 represent a 5 to 6 member saturated ring containing up to one other
 heteroatom selected from oxygen and nitrogen, where the ring is
 optionally substituted with one or more substituents selected from amino,
 35 methylamino and dimethylamino,

where R² and R³ are independently hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and n is 0-2; and

5 R⁷ is hydrogen;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

10 Included among the presently invented compounds of Formula (II) are those in which:

15 R¹ is selected from: alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl containing from 1 to 3 heteroatoms and C₁-C₁₂aryl;

20 R⁴ is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C₁-C₁₂aryl and C₁-C₁₂aryl substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryloxy, hydroxy, alkoxy, acyloxy, amino, N-acylamino, nitro, cyano and halogen; and

R⁷ is selected from hydrogen, -C(O)NR⁹R¹⁰ and -(CH₂)_nOR⁸, where n is 0-2;

25 R⁸ is alkyl, piperidine, imidazolidine, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, hydroxy, nitro, cyano, cycloalkyl, halogen and C₁-C₁₂aryl,

30 R⁹ and R¹⁰ are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C₁-C₁₂aryl, substituted cycloalkyl, substituted C₁-C₁₂aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, -NR²R³, nitro, cyano, cycloalkyl, halogen, aryl and substituted aryl, or R⁹ and R¹⁰ taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is

35

optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1 - C_{12} aryl, substituted alkyl, substituted cycloalkyl and substituted C_1 - C_{12} aryl;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the presently invented compounds of Formula (III) are those in which:

R^1 is selected from: alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl containing from 1 to 3 heteroatoms and C_1 - C_{12} aryl;

R^4 is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C_1 - C_{12} aryl and C_1 - C_{12} aryl substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryloxy, hydroxy, alkoxy, acyloxy, amino, N-acylamino, nitro, cyano and halogen; and

R^7 is selected from $-C(O)NR^9R^{10}$ and $-(CH_2)_nOR^8$, where n is 0-2;

R^8 is alkyl, piperidine, imidazolidine, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, hydroxy, nitro, cyano, cycloalkyl, halogen and C_1 - C_{12} aryl,

R^9 and R^{10} are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C_1 - C_{12} aryl, substituted cycloalkyl, substituted C_1 - C_{12} aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, $-NR^2R^3$, nitro, cyano, cycloalkyl, halogen, aryl and substituted aryl, or R^9 and R^{10} taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is

optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R² and R³ are independently hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the presently invented compounds of Formula (IV) are those in which:

R¹ is selected from: alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy; amino, N-acylamino, cyclopropyl and halogen, cycloalkyl containing from 1 to 3 heteroatoms and C₁-C₁₂aryl;

R⁴ is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C₁-C₁₂aryl and C₁-C₁₂aryl substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryloxy, hydroxy, alkoxy, acyloxy, amino, N-acylamino, nitro, cyano and halogen; and

R⁷ is hydrogen;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the compounds useful in the present invention are:

4-(4-Phenyl-1-piperidin-4-yl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine;

4-[4-(3-Chloro-phenyl)-1-piperidin-4-yl-1H-imidazo-[4,5-c]pyridin-2-yl]furazan-3-ylamine;

4-[1-(3-Amino-2,2-dimethylpropyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine;

4-[1-(cyclopropylmethyl)-4-(2-methylphenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

4-[4-(2-chlorophenyl)-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

- 4-[1-(3-Amino-2,2-dimethylpropyl)-4-phenyl-1H-imidazo[4,5-c]pyridinyl-2-yl]-
furazan-3-ylamine;
- 4-[4-(3-chlorophenyl)-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-
oxadiazol-3-amine;
- 5 4-[4-chloro-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-
amine;
- 4-[1-(cyclopropylmethyl)-4-(3-furanyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-
oxadiazol-3-amine;
- 4-[1-(5-aminopentyl)-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-
amine;
- 10 4-[1-(6-aminohexyl)-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-
amine;
- 4-[1-(5-aminopentyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-
oxadiazol-3-amine;
- 15 4-[1-(6-aminohexyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-
oxadiazol-3-amine;
- 4-[1-(3-Amino-2,2-dimethylpropyl)-4-(3-methoxyphenyl)-1H-imidazo[4,5-c]pyridinyl-
2-yl]-furazan-3-ylamine;
- 4-[1-(5-aminopentyl)-4-(3-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-
amine;
- 20 4-[1-(6-aminohexyl)-4-(3-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-
amine;
- 25 4-[4-phenyl-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-
amine;
- 4-[4-(3-chlorophenyl)-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-
oxadiazol-3-amine;
- 4-[4-(4-chlorophenyl)-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-
oxadiazol-3-amine;
- 30 4-[1-(3-aminopropyl)-4-(2-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-
amine;
- 4-[1-(3-aminopropyl)-4-(1-piperidinyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-
oxadiazol-3-amine;
- 35

- 1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-phenyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;
- 1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-thiophen-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;
- 5 1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-pyridin-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;
- 1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-pyridin-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;
- 1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-furan-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;
- 10 1-[2-(4-Amino-furazan-3-yl)-4-chloro-1-ethyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;
- 1-[2-(4-Amino-furazan-3-yl)-4-(1H-pyrrol-2-yl))-1-ethyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;
- 15 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-methoxyphenyl)-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;
- 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-(3-chloro-phenyl)-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;
- 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-furan-2-yl-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;
- 20 2-(4-Amino-furazan-3-yl)-1-ethyl-4-phenyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;
- 2-(4-Amino-furazan-3-yl)-1-ethyl-4-(3-chloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;
- 25 2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2,3-dichloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;
- 2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-chloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;
- 2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-hydroxy-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;
- 30 2-(4-Amino-furazan-3-yl)-4-(3-chloro-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
- 2-(4-Amino-furazan-3-yl)-4-phenyl-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
- 35 2-(4-Amino-furazan-3-yl)-4-(5-chloro-thiophen-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

- 2-(4-Amino-furazan-3-yl)-4-(2-amino-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
- 2-(4-Amino-furazan-3-yl)-4-(3-amino-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
- 5 2-(4-Amino-furazan-3-yl)-4-(3-bromo-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
- 2-(4-Amino-furazan-3-yl)-4-(1-naphthalenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
- 10 2-(4-Amino-furazan-3-yl)-4-(thiophen-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
- 2-(4-Amino-furazan-3-yl)-4-(3,4-methylenedioxyphenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
- 2-(4-Amino-furazan-3-yl)-4-(3,5-dichloro-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
- 15 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
- 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(4-biphenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
- 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2,4-dichlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
- 20 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-(phenylethynyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
- 2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol;
- 25 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2-chlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
- (2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenyl)methanol;
- 2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}-4-chlorophenol;
- 30 4-(1-ethyl-7-[[3-(methylamino)-1-pyrrolidinyl]carbonyl]-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;
- 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-(4-methylphenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
- 35 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2,5-dichlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

- 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(1-benzothien-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
 4-[1-ethyl-4-phenyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
 5 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-[4-(methyloxy)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
 4-[2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl]phenol;
 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(4-chlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
 10 4-[4-(3-chlorophenyl)-1-ethyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
 2-(4-amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-N-{2-[(phenylmethyl)amino]ethyl}-1H-imidazo[4,5-c]pyridine-7-carboxamide;
 15 4-[1-Ethyl-7-(piperidin-4-yloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine
 3-[2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl]phenol;
 4-[2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl]benzonitrile;
 20 1-[2-(4-Amino-furazan-3-yl)-4-phenyl-1-piperidin-4-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;
 4-(4-(3-chlorophenyl)-1-ethyl-7-[[3-(methylamino)-1-pyrrolidinyl]carbonyl]-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;
 4-(4-(2,5-dichlorophenyl)-1-ethyl-7-[[3-(methylamino)-1-pyrrolidinyl]carbonyl]-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;
 25 4-[4-(2,5-dichlorophenyl)-1-ethyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine; and
 2-(4-amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-N-[3-(dimethylamino)propyl]-1H-imidazo[4,5-c]pyridine-7-carboxamide;
 30 and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention.

- By the term "protected hydroxy" or "protected -OH" as used herein, is meant
 35 the alcoholic or carboxylic-OH groups which can be protected by conventional blocking groups in the art such as described in "Protective Groups In Organic Synthesis" by Theodora W. Greene, Wiley-Interscience, 1981, New York.

Compounds containing protected hydroxy groups may also be useful as intermediates in the preparation of the pharmaceutically active compounds of the invention.

By the term "aryl" as used herein, unless otherwise defined, is meant a cyclic or polycyclic aromatic ring containing from 1 to 14 carbon atoms and optionally containing from one to five heteroatoms, provided that when the number of carbon atoms is 1 the aromatic ring contains at least four heteroatoms, when the number of carbon atoms is 2 the aromatic ring contains at least three heteroatoms, when the number of carbons is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom.

By the term "C₁-C₁₂aryl" as used herein, unless otherwise defined, is meant phenyl, naphthalene, 3,4-methylenedioxyphenyl, pyridine, biphenyl, quinoline, pyrimidine, quinazoline, thiophene, furan, pyrrole, pyrazole, imidazole benzothiohene and tetrazole.

The term "substituted" as used herein, unless otherwise defined, is meant that the subject chemical moiety has one or more substituents selected from the group consisting of: -CO₂R²⁰, aryl, -C(O)NHS(O)₂R²⁰, -NHS(O)₂R²⁰, hydroxyalkyl, alkoxy, -C(O)NR²¹R²², acyloxy, alkyl, amino, methylamino, dimethylamino, N-acylamino, hydroxy, -(CH₂)_gC(O)OR²³, -S(O)_nR²³, nitro, tetrazole, cyano, oxo, halogen, trifluoromethyl and protected -OH, where g is 0-6, R²³ is hydrogen or alkyl, R²⁰ is selected from hydrogen, C₁-C₄alkyl, aryl and trifluoromethyl, and R²¹ and R²² are independently selected from hydrogen, C₁-C₄alkyl, aryl and trifluoromethyl, and n is 0-2.

By the term "alkoxy" as used herein is meant -Oalkyl where alkyl is as described herein including -OCH₃ and -OC(CH₃)₂CH₃.

The term "cycloalkyl" as used herein unless otherwise defined, is meant a nonaromatic, unsaturated or saturated, cyclic or polycyclic C₃-C₁₂.

Examples of cycloalkyl and substituted cycloalkyl substituents as used herein include: cyclohexyl, 4-hydroxy-cyclohexyl, 2-ethylcyclohexyl, propyl 4-methoxycyclohexyl, 4-methoxycyclohexyl, 4-carboxycyclohexyl, cyclopropyl and cyclopentyl.

By the term "acyloxy" as used herein is meant -OC(O)alkyl where alkyl is as described herein. Examples of acyloxy substituents as used herein include: -OC(O)CH₃, -OC(O)CH(CH₃)₂ and -OC(O)(CH₂)₃CH₃.

By the term "N-acylamino" as used herein is meant -N(H)C(O)alkyl, where alkyl is as described herein. Examples of N-acylamino substituents as used herein include: -N(H)C(O)CH₃, -N(H)C(O)CH(CH₃)₂ and -N(H)C(O)(CH₂)₃CH₃.

5 By the term "aryloxy" as used herein is meant -Oaryl where aryl is phenyl, naphthyl, 3,4-methylenedioxyphenyl, pyridyl or biphenyl optionally substituted with one or more substituents selected from the group consisting of: alkyl, hydroxyalkyl, alkoxy, trifluoromethyl, acyloxy, amino, N-acylamino, hydroxy, -(CH₂)_gC(O)OR²⁵, -S(O)_nR²⁵, nitro, cyano, halogen and protected -OH, where g is 0-6, R²⁵ is hydrogen or alkyl, and n is 0-2. Examples of aryloxy substituents as used herein
10 include: phenoxy, 4-fluorophenyloxy and biphenyloxy.

By the term "heteroatom" as used herein is meant oxygen, nitrogen or sulfur.

By the term "halogen" as used herein is meant a substituent selected from bromide, iodide, chloride and fluoride.

15 By the term "alkyl" and derivatives thereof and in all carbon chains as used herein is meant a linear or branched, saturated or unsaturated hydrocarbon chain, and unless otherwise defined, the carbon chain will contain from 1 to 12 carbon atoms. Examples of alkyl substituents as used herein include: -CH₃, -CH₂-CH₃, -CH₂-CH₂-CH₃, -CH(CH₃)₂, -C(CH₃)₃, -(CH₂)₃-CH₃, -CH₂-CH(CH₃)₂,
20 -CH(CH₃)-CH₂-CH₃, -CH=CH₂, and -C≡C-CH₃.

By the term "treating" and derivatives thereof as used herein, is meant prophylactic and therapeutic therapy.

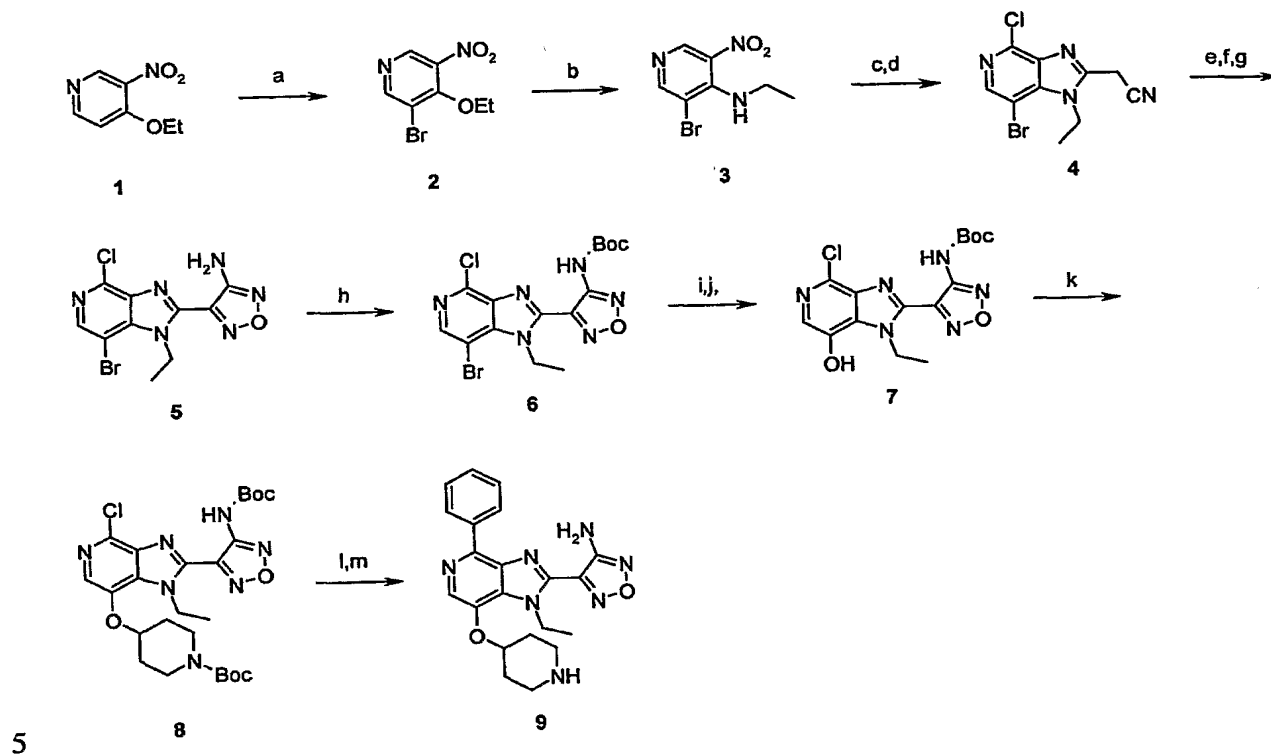
All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set
25 forth.

Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention. Where a -COOH or -OH group is present, pharmaceutically acceptable esters can be employed, for example methyl, ethyl, pivaloyloxymethyl, and the like for -COOH, and acetate
30 maleate and the like for -OH, and those esters known in the art for modifying solubility or hydrolysis characteristics, for use as sustained release or prodrug formulations.

The novel compounds of Formulas I, II, III and IV are prepared as shown in Schemes I to III below, or by analogous methods, wherein the 'Het' and 'R'
35 substituents are as defined in Formulas I, II, III and IV respectively and provided that the 'Het' and 'R' substituents do not include any such substituents that render inoperative the processes of Schemes I to IV. All of the starting materials are

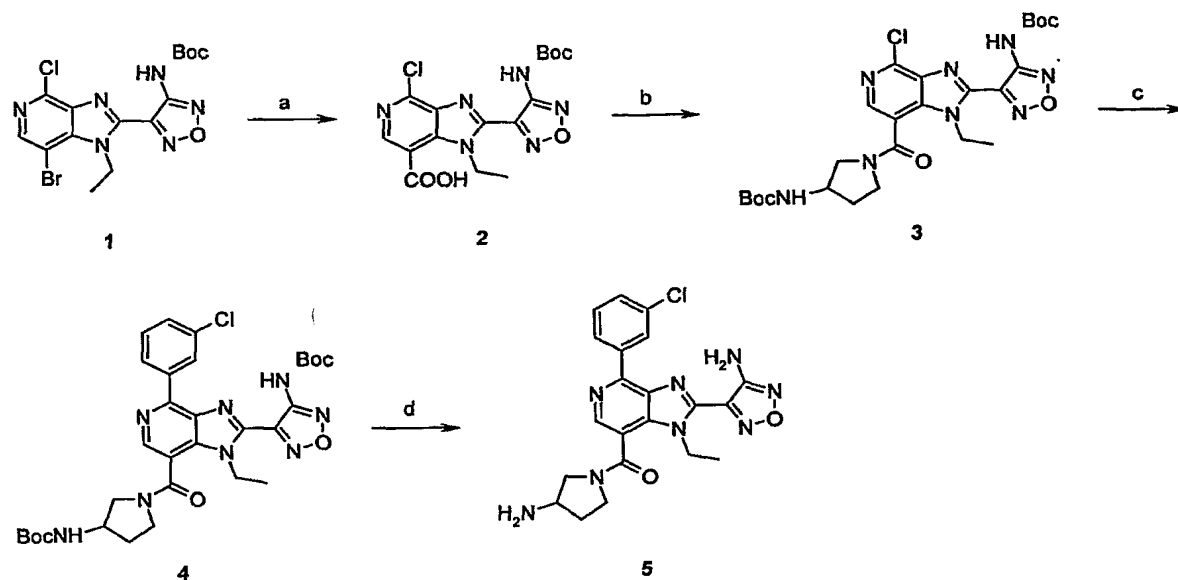
commercially available or are readily made from commercially available starting materials by those of skill in the art.

SCHEME 1



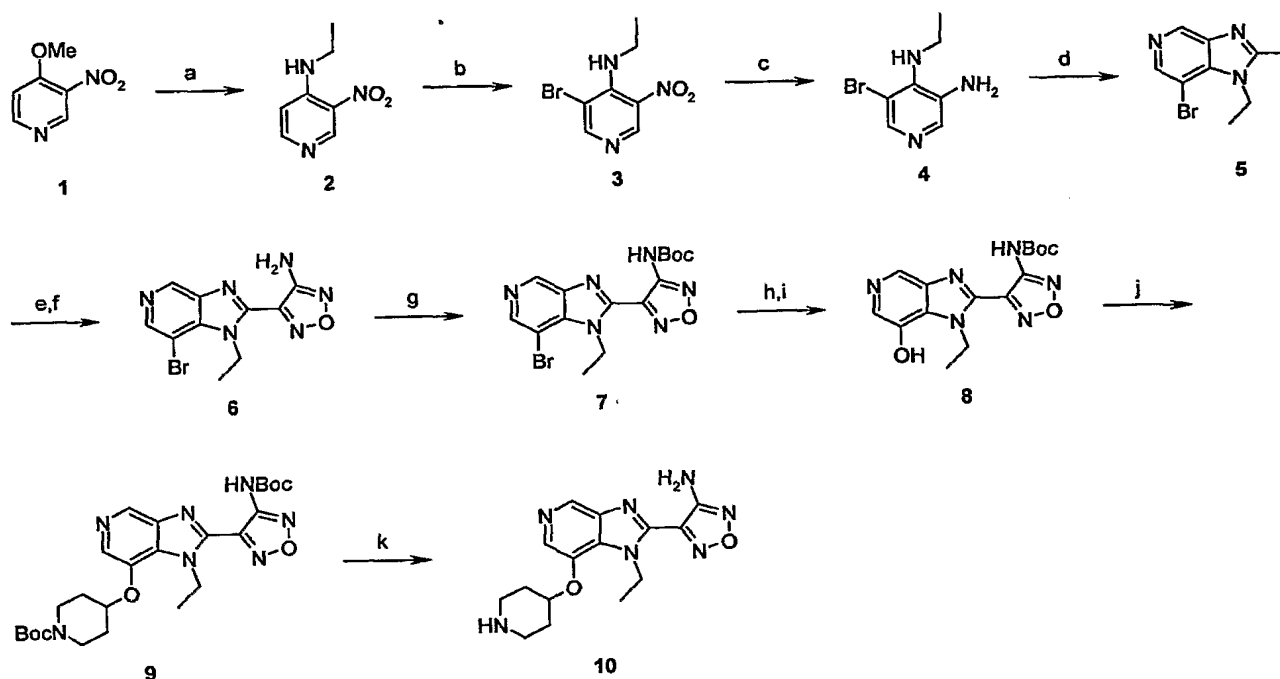
- (a) Br_2 , NaOAc, AcOH, 60 °C; (b) EtNH_2 ; (c) SnCl_2 , HCl; (d) ethyl cyanoacetate, 190 °C; (e) NaNO_2 , HCl; (f) NH_2OH ; (g) Et_3N , dioxane, 150 °C; (h) di-*t*-butyldicarbonate, DMAP, pyridine; (i) i - $n\text{-BuLi}$, -78 °C. ii - B(OMe)_3 ; (j) H_2O_2 , NaOH; (k) 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate, polymer-bound Ph_3P , DEAD, $\text{CH}_2\text{Cl}_2/\text{THF}$; (l) PhB(OH)_2 , $(\text{Ph}_3\text{P})_4\text{Pd}$, 2M Na_2CO_3 , toluene/EtOH; (m) TFA, CH_2Cl_2 .

SCHEME 2



(a) i - n-BuLi, ii - CO₂; (b) 1,1-dimethylethyl 3-pyrrolidinylcarbamate, EDCI, HOAt, NMM; (c) (3-chlorophenyl)B(OH)₂, (Ph₃P)₄Pd, 2M Na₂CO₃, toluene; (d) TFA.

SCHEME 3



- 5 (a) EtNH₂; (b) Br₂, NaOAc, AcOH; (c) Fe powder, AcOH; (d) ethyl cyanoacetate, 190 °C; (e) NaNO₂; (f) NH₂OH; (g) di-*t*-butyldicarbonate, DMAP, pyridine; (h) *i*-n-BuLi, ii - B(OMe)₃; (i) H₂O₂, NaOH; (j) 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate, polymer-bound Ph₃P, DEAD, CH₂Cl₂; (k) TFA.

10 By the term "co-administering" and derivatives thereof as used herein is meant either simultaneous administration or any manner of separate sequential administration of an AKT inhibiting compound, as described herein, and a further active ingredient or ingredients, known to be useful in the treatment of cancer, including chemotherapy and radiation treatment, or to be useful in the treatment of arthritis. The term further active ingredient or ingredients, as used herein, includes any compound or therapeutic agent known to or that demonstrates advantageous properties when administered to a patient in need of treatment for cancer or arthritis. Preferably, if the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and another compound may be administered orally.

Examples of a further active ingredient or ingredients for use in combination with the presently invented Akt inhibiting compounds are chemotherapeutic agents.

5 Because the pharmaceutically active compounds of the present invention are active as Akt inhibitors they exhibit therapeutic utility in treating cancer and arthritis.

Compounds of the invention are tested for potency as Akt inhibitors by known methods, such as described in International Application No. PCT/US02/10880.

10 The pharmaceutically active compounds within the scope of this invention are useful as Akt inhibitors in mammals, particularly humans, in need thereof.

 The present invention therefore provides a method of treating cancer, arthritis and other conditions requiring Akt inhibition, which comprises administering an effective compound of Formula (I) or a pharmaceutically acceptable salt,
15 hydrate, solvate or ester thereof. The compounds of Formula (I) also provide for a method of treating the above indicated disease states because of their demonstrated ability to act as Akt inhibitors. The drug may be administered to a patient in need thereof by any conventional route of administration, including, but not limited to, intravenous, intramuscular, oral, subcutaneous, intradermal, and
20 parenteral.

 The pharmaceutically active compounds of the present invention are incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers are employed. Solid carriers include, starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin,
25 agar, pectin, acacia, magnesium stearate, and stearic acid;. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid
30 carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampoule, or an aqueous or nonaqueous liquid suspension.

 The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and
35 compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

Doses of the presently invented pharmaceutically active compounds in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity preferably selected from the range of 0.001 - 100 mg/kg of active compound, preferably 0.001 - 50 mg/kg. When treating a human patient in need of an Akt inhibitor, the selected dose is administered preferably from 1-6 times daily, orally or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermally, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 0.05 to 3500 mg of active compound. Oral administration, which uses lower dosages is preferred. Parenteral administration, at high dosages, however, also can be used when safe and convenient for the patient.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular Akt inhibitor in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular patient being treated will result in a need to adjust dosages, including patient age, weight, diet, and time of administration.

The method of this invention of inducing Akt inhibitory activity in mammals, including humans, comprises administering to a subject in need of such activity an effective Akt inhibiting amount of a pharmaceutically active compound of the present invention.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use as an Akt inhibitor.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in therapy.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating cancer.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating arthritis.

The invention also provides for a pharmaceutical composition for use as an Akt inhibitor which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in the treatment of cancer which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in treating arthritis which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

5 No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

In addition, the pharmaceutically active compounds of the present invention can be co-administered with further active ingredients, such as other compounds known to treat cancer or arthritis, or compounds known to have utility when used in combination with an Akt inhibitor.

10 Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

15

Experimental Details

The compounds of Examples 1 to 72 are readily made according to Schemes I to III or by analogous methods.

20

Example 1

4-(4-Phenyl-1-piperidin-4-yl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine;

25

Example 2

4-[4-(3-Chloro-phenyl)-1-piperidin-4-yl-1H-imidazo-[4,5-c]pyridin-2-yl]furazan-3-ylamine;

30

Example 3

4-[1-(3-Amino-2,2-dimethylpropyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine;

35

Example 4

4-[1-(cyclopropylmethyl)-4-(2-methylphenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

5

Example 5

4-[4-(2-chlorophenyl)-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

10

Example 6

4-[1-(3-Amino-2,2-dimethylpropyl)-4-phenyl-1H-imidazo[4,5-c]pyridinyl-2-yl]-furazan-3-ylamine;

15

Example 7

4-[4-(3-chlorophenyl)-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

20

Example 8

4-[4-chloro-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

25

Example 9

4-[1-(cyclopropylmethyl)-4-(3-furanyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

30

Example 10

4-[1-(5-aminopentyl)-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

35

Example 11

4-[1-(6-aminohexyl)-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

5

Example 12

4-[1-(5-aminopentyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

10

Example 13

4-[1-(6-aminohexyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

15

Example 14

4-[1-(3-Amino-2,2-dimethylpropyl)-4-(3-methoxyphenyl)-1H-imidazo[4,5-c]pyridinyl-2-yl]-furazan-3-ylamine;

20

Example 15

4-[1-(5-aminopentyl)-4-(3-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

25

Example 16

4-[1-(6-aminohexyl)-4-(3-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

30

Example 17

4-[4-phenyl-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

35

Example 18

4-[4-(3-chlorophenyl)-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

5

Example 19

4-[4-(4-chlorophenyl)-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

10

Example 20

4-[1-(3-aminopropyl)-4-(2-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

15

Example 21

4-[1-(3-aminopropyl)-4-(1-piperidinyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

20

Example 22

1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-phenyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;

25

Example 23

1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-thiophen-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;

30

Example 24

1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-pyridin-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;

35

Example 25

5 1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-pyridin-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;

Example 26

10 1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-furan-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;

Example 27

15 1-[2-(4-Amino-furazan-3-yl)-4-chloro-1-ethyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

Example 28

20 1-[2-(4-Amino-furazan-3-yl)-4-(1H-pyrrol-2-yl))-1-ethyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

Example 29

25 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-methoxyphenyl)-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

Example 30

30 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-(3-chloro-phenyl)-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

Example 31

35 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-furan-2-yl-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

Example 32

2-(4-Amino-furazan-3-yl)-1-ethyl-4-phenyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;

5

Example 33

2-(4-Amino-furazan-3-yl)-1-ethyl-4-(3-chloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;

10

Example 34

2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2,3-dichloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;

15

Example 35

2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-chloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;

20

Example 36

2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-hydroxy-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;

25

Example 37

2-(4-Amino-furazan-3-yl)-4-(3-chloro-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

30

Example 38

2-(4-Amino-furazan-3-yl)-4-phenyl-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

35

Example 39

2-(4-Amino-furazan-3-yl)-4-(5-chloro-thiophen-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

5

Example 40

2-(4-Amino-furazan-3-yl)-4-(2-amino-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

10

Example 41

2-(4-Amino-furazan-3-yl)-4-(3-amino-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

15

Example 42

2-(4-Amino-furazan-3-yl)-4-(3-bromo-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

20

Example 43

2-(4-Amino-furazan-3-yl)-4-(1-naphthalenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

25

Example 44

2-(4-Amino-furazan-3-yl)-4-(thiophen-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

30

Example 45

2-(4-Amino-furazan-3-yl)-4-(3,4-methylenedioxyphenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

35

Example 46

2-(4-Amino-furazan-3-yl)-4-(3,5-dichloro-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

5

Example 47

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

10

Example 48

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(4-biphenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

15

Example 49

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2,4-dichlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

20

Example 50

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-(phenylethynyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

25

Example 51

2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol;

30

Example 52

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2-chlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

35

Example 53

(2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenyl)methanol;

5

Example 54

2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}-4-chlorophenol;

10

Example 55

4-(1-ethyl-7-[(3-(methylamino)-1-pyrrolidinyl)carbonyl]-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;

15

Example 56

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-(4-methylphenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

20

Example 57

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2,5-dichlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

25

Example 58

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(1-benzothien-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

30

Example 59

4-[1-ethyl-4-phenyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

35

Example 60

4-{7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-[4-(methyloxy)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-1,2,5-oxadiazol-3-amine;

5

Example 61

4-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol;

10

Example 62

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(4-chlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

15

Example 63

4-[4-(3-chlorophenyl)-1-ethyl-7-(4-piperidinylloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

20

Example 64

2-(4-amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-N-{2-[(phenylmethyl)amino]ethyl}-1H-imidazo[4,5-c]pyridine-7-carboxamide;

25

Example 65

4-[1-Ethyl-7-(piperidin-4-yloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine;

30

Example 66

3-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol;

35

Example 67

4-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}benzonitrile;

5

Example 68

1-[2-(4-Amino-furazan-3-yl)-4-phenyl-1-piperidin-4-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

10

Example 69

4-(4-(3-chlorophenyl)-1-ethyl-7-[(3-(methylamino)-1-pyrrolidinyl)carbonyl]-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;

15

Example 70

4-(4-(2,5-dichlorophenyl)-1-ethyl-7-[(3-(methylamino)-1-pyrrolidinyl)carbonyl]-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;

20

Example 71

4-[4-(2,5-dichlorophenyl)-1-ethyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

25

Example 72

2-(4-amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-N-[3-(dimethylamino)propyl]-1H-imidazo[4,5-c]pyridine-7-carboxamide;

30

Example 73- Capsule Composition

An oral dosage form for administering the present invention is produced by filing a standard two piece hard gelatin capsule with the ingredients in the proportions shown in Table I, below.

35

Table I

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
4-(4-Phenyl-1-piperidin-4-yl)-1H-imidazo[4,5-c]pyridin-2-yl)- furazan-3-ylamine	25 mg
Lactose	55 mg
Talc	16 mg
Magnesium Stearate	4 mg

Example 74 - Injectable Parenteral Composition

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An injectable form for administering the present invention is produced by stirring 1.5% by weight of 1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-phenyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone in 10% by volume propylene glycol in water.

10

Example 75 - Tablet Composition

15 The sucrose, calcium sulfate dihydrate and an Akt inhibitor as shown in Table II below, are mixed and granulated in the proportions shown with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid; screened and compressed into a tablet.

Table II

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
2-(4-amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-((cyclopropylmethyl)-N-[3-(dimethylamino)propyl]-1H- imidazo[4,5-c]pyridine-7-carboxamide	20 mg
calcium sulfate dihydrate	30 mg
sucrose	4 mg
starch	2 mg
talc	1 mg
stearic acid	0.5 mg

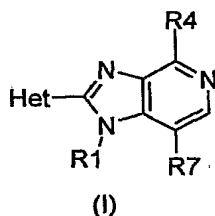
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While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

What is claimed is:

1. A compound of Formula (I):

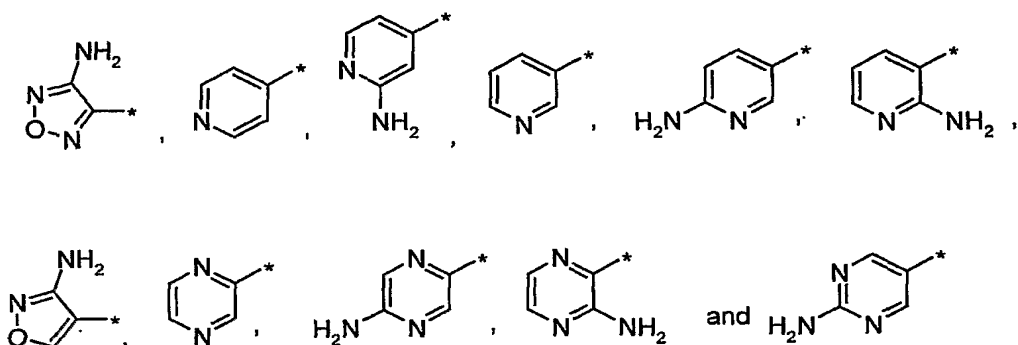
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wherein:

Het is selected from the group consisting of:

10



15

R¹ is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, C₁-C₁₂aryl and C₁-C₁₂aryl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

25

R^4 is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, $-C(O)OR^2$, $-C(O)NR^5R^6$, $-S(O)_2NR^5R^6$, $-S(O)_nR^2$ and protected $-OH$, where n is 0-2,

R^2 is hydrogen, alkyl, cycloalkyl, C_1 - C_{12} aryl, substituted alkyl, substituted cycloalkyl and substituted C_1 - C_{12} aryl, and

R^5 and R^6 are independently hydrogen, cycloalkyl, C_1 - C_{12} aryl, substituted cycloalkyl, substituted C_1 - C_{12} aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^2$, $-S(O)_nR^2$, $-C(O)NR^2R^3$, $-S(O)_2NR^2R^3$, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected $-OH$, or R^5 and R^6 taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R^2 and R^3 are independently hydrogen, alkyl, cycloalkyl, C_1 - C_{12} aryl, substituted alkyl, substituted cycloalkyl and substituted C_1 - C_{12} aryl, and n is 0-2; and

R^7 is selected from hydrogen, $-C(O)NR^9R^{10}$, $-(CH_2)_nNR^9R^{10}$, $-SO_2NR^9R^{10}$ and $-(CH_2)_nOR^8$, where n is 0-2;

R^8 is alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, $-C(O)OR^2$, $-S(O)_nR^2$,

-C(O)NR²R³, -S(O)₂NR²R³, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH,

where R² and R³ are independently hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and n is 0-2,

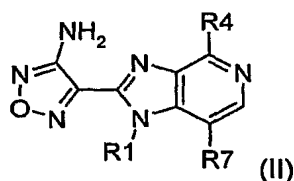
R⁹ and R¹⁰ are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C₁-C₁₂aryl, substituted cycloalkyl, substituted C₁-C₁₂aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, -C(O)OR², -S(O)_nR², -C(O)NR²R³, -S(O)₂NR²R³, -NR²R³, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH,

or R⁹ and R¹⁰ taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R² and R³ are independently hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and n is 0-2.

2. A pharmaceutically acceptable salt, hydrate, solvate or ester of a compound of Formula (I), as described in claim 1.

3. A compound of Claim 1 represented by the following Formula (II):



wherein:

R¹ is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy,

amino, N-acylamino, cyclopropyl and halogen, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, C₁-C₁₂aryl and C₁-C₁₂aryl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

R⁴ is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, -C(O)OR², -C(O)NR⁵R⁶, -S(O)₂NR⁵R⁶, -S(O)_nR² and protected -OH, where n is 0-2,

R² is hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and

R⁵ and R⁶ are independently hydrogen, cycloalkyl, C₁-C₁₂aryl, substituted cycloalkyl, substituted C₁-C₁₂aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, -C(O)OR², -S(O)_nR², -C(O)NR²R³, -S(O)₂NR²R³, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH, or R⁵ and R⁶ taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R² and R³ are independently hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and n is 0-2; and

5 R⁷ is selected from hydrogen, -C(O)NR⁹R¹⁰, -(CH₂)_nNR⁹R¹⁰, -SO₂NR⁹R¹⁰ and -(CH₂)_nOR⁸,

where n is 0-2;

R⁸ is alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, piperidyl and pyrrolidinyl, each of which is optionally substituted with one
10 or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, -C(O)OR², -S(O)_nR², -C(O)NR²R³, -S(O)₂NR²R³, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH,

15 where R² and R³ are independently hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and n is 0-2,

R⁹ and R¹⁰ are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C₁-C₁₂aryl, substituted cycloalkyl, substituted C₁-C₁₂aryl, alkyl or alkyl substituted with one or more substituents
20 selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, -C(O)OR², -S(O)_nR², -C(O)NR²R³, -S(O)₂NR²R³, -NR²R³, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH,

25 or R⁹ and R¹⁰ taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

30 where R² and R³ are independently hydrogen, alkyl, cycloalkyl, C₁-C₁₂aryl, substituted alkyl, substituted cycloalkyl and substituted C₁-C₁₂aryl, and n is 0-2.

35 4. A pharmaceutically acceptable salt, hydrate, solvate or ester of a compound of Formula (II), as described in claim 3.

ABSTRACT OF THE DISCLOSURE

Invented are novel 1H-imidazo[4,5-c]pyridin-2-yl compounds, the use of such compounds as inhibitors of PKB/AKT kinase activity and in the treatment of cancer and arthritis.